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EXAMINER

SPECTOR, L

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LEGAL AFFAIRS DEPARTMENT  
IMMUNEX CORPORATION  
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1812

DATE MAILED:

12/09/94

This is a communication from the examiner in charge of your application.  
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on \_\_\_\_\_ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.  
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

**Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:**

- |   |   |
|---|---|
| 1. <input checked="" type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input type="checkbox"/> Notice of Draftsman's Patent Drawing Review, PTO-948. |
| 3. <input type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449.                 | 4. <input type="checkbox"/> Notice of Informal Patent Application, PTO-152.       |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474.     | 6. <input type="checkbox"/> _____   |

**Part II SUMMARY OF ACTION**

1. ☒ Claims 1-67 are pending in the application.  
Of the above, claims 1-12, 44-67 are withdrawn from consideration.
2. ☐ Claims \_\_\_\_\_ have been cancelled.
3. ☐ Claims \_\_\_\_\_ are allowed.
4. ☒ Claims 13-43 are rejected.
5. ☐ Claims \_\_\_\_\_ are objected to.
6. ☒ Claims 1-67 are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on \_\_\_\_\_. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on \_\_\_\_\_, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed \_\_\_\_\_, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received  
☐ been filed in parent application, serial no. \_\_\_\_\_; filed on \_\_\_\_\_.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

**Part III: Detailed Office Action**

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

- I. Claims 1-12, drawn to flt3-ligand, classified in Class 530, subclasses 350 or 399.
- 5 II. Claims 13-43, drawn to DNA, vectors and host cells, classified in Class 536, subclass 23.5 and Class 435, subclasses 240.1, 320.1 and 252.3.
- 10 III. Claims 44 and 45, drawn to anti-flt3/flk2-L antibodies, classified in Class 530, subclass 387.7.
- 15 IV. Claim 46, drawn to antisense oligonucleotides, classified in Class 536, subclass 24.5.
- V. Claims 47 and 48, drawn to a flt3/flk2-Ig fusion protein, classified in Class 435, subclass 69.7.
- 20 VI. Claims 49-53, drawn to compositions comprising flt3-L and IL7, classified in Class 424, subclass 85.2.
- VII. Claims 54-58, drawn to compositions comprising flt3-L and IL3, classified in Class 424, subclass 85.2.
- 25 VIII. Claims 59-62, drawn to an autologous transplantation method, classified in Class 424, subclass 93.7.
- IX. Claims 63-65, drawn to growth medium comprising flt3-L, classified in Class 435, subclass 240.2.
- 30 X. Claim 66, drawn to a transfection method, classified in Class 435, subclass 172.1.
- XI. Claim 67, drawn to a gene therapy method, classified in Class 424, subclass 93.21.

The inventions are distinct, each from the other because of the following reasons:

The nucleic acids of Invention II are related to the protein of Invention I by virtue of encoding same. The DNA molecule has utility for the recombinant production of the protein in

a host cell. Although the DNA molecule and protein are related since the DNA encodes the specifically claimed protein, they are distinct inventions because the protein product can be made by another and materially different process, such as by synthetic peptide synthesis or purification from the natural source. Further, the DNA may be used for processes other than the production of the protein, such as nucleic acid hybridization assay.

The proteins of Invention I are related to the antibodies of Invention III by virtue of being the cognate antigen, necessary for the production of the antibodies. Although the protein and antibody are related due to the necessary steric complementarity of the two, they are distinct inventions because the protein can be used another and materially different process from the use for production of the antibody, such as in a pharmaceutical or cell growth composition in its own right, or to assay or purify the cognate receptor (as the protein is itself a ligand), or in assays for the identification of agonists or antagonists of the receptor protein.

Inventions I, IV and V are drawn to <sup>physically, functionally, and patentably</sup> distinct products wherein each product does not require the others, the products have different uses and means of manufacture, and the products require non-coextensive searches.

Inventions VI and VII and IX are related to invention I as compositions which require the protein of invention I. However, these compositions are separate and distinct from the protein itself, having different uses and requiring non-coextensive searches. Similarly the compositions of Inventions VI and VII are distinct from each other due to the requirement for patentably distinct interleukins, and require non-coextensive searches. These compositions are distinct from the composition of Invention IX, wherein the compositions require different components and have distinct uses, requiring non-coextensive searches.

Inventions I, VI and VII are each related to each of inventions VIII, X and XI as products and processes of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the processes

of use can use any of the three products, and the products can be used in any of the distinct methods of Inventions VIII, X or XI, or alternatively for the purification of flt3 protein or for the identification of agonists or antagonists of flt3.

5 The nucleic acids, vectors and host cells of Invention II, antibodies of invention III, fusion proteins of invention V, and compositions of inventions VI and VII constitute distinct products wherein each product does not require the others, the products have different uses and means of manufacture, and the products require non-coextensive searches.

10 The antisense oligonucleotides of Invention IV are related to the nucleic acids of Invention II by virtue of being subsequences of longer disclosed sequences. However, these inventions are patentably distinct because they are used in materially different processes which processes are completely different and distinct. The arts of antisense therapy and recombinant production of proteins are separate and distinct, and require non-coextensive searches.

15 Each of the products of inventions II-V are distinct and unrelated to each of the methods of inventions VIII, X and XI, wherein none of the methods requires any of the products, and the inventions require non-coextensive searches. The products of inventions II-V are distinct and unrelated to the product of invention IX, wherein invention IX does not require any of the products of inventions II-V, and the inventions require non-coextensive searches.

20 The antisense oligonucleotides of invention IV and compositions of inventions VI and VII constitute distinct products wherein each product does not require the others, the products have different uses and means of manufacture, and the products require non-coextensive searches.

25 Invention IX is related to each of inventions VIII, X and XI as product and processes of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the product may be used in any of the materially different methods of the cited inventions, or alternatively for the *in vitro* maintenance of cell culture lines.

The method of Invention VIII is distinct from the methods of inventions X and XI, wherein each does not require the others, and the inventions require non-coextensive searches.

The methods of Inventions X and XI are related because invention XI requires the steps of invention X. However, these two methods are nonetheless distinct because they have different endpoints, have substantially different uses, and the inventions require non-coextensive searches.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and recognized divergent subject matter, *and the search and examination of each would be unduly burdensome, therefore,* restriction for examination purposes as indicated is proper.

During a telephone conversation with Stephen Malaska on 9/28/94 a provisional election was made with traverse to prosecute the invention of group II, claims 13-43. Affirmation of this election must be made by applicant in responding to this Office action. Claims 1-12 and 44-67 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

The disclosure is objected to because of the following informalities; Appropriate correction is required:

(1) Table IV, at page 40 of the specification, is incorrect. Specifically, it appears that the heading "ng/ml" is correct, however the numbers in that column are in a format usually used for dilution factors; the "1:" should be deleted from all entries in that column.

(2) At page 24, line 29 "it's" should read --its--; at line 30, "product's" should read either --products-- or --products'--.

The Examiner notes that there are likely to be provisional double patenting rejections appropriate between the claims of the instant application and the claims of copending application Serial Number 08/111,758. However, the copending application is not available to the Examiner at this time, so the determination of double patenting can not be made. Applicants are advised that provisional double patenting or obvious double patenting rejections will be made where applicable to the claims in this application, and are advised to take appropriate action.

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. *In re Vogel*, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

Example 7 is ambiguous; the text indicates that three species of the ligand were used in the experiments, whereas it is not indicated whether the data presented in Tables 1 and 2 represent an experiment with only one of the three species (and if so, which) or whether results from all three species are represented, and whether all three species gave analogous results. Applicants are reminded in amending the specification to avoid the introduction of new matter.

Enablement of the current specification as filed is not commensurate in scope with claims

to nucleic acids encoding any and all possible ligands of the flt3/flk2 receptor. The current specification enables only nucleic acids encoding a single such ligand, obtained from mouse and human cell lines. It is well known in the art that receptors may have multiple ligands, especially, as in the current case, when the receptors are expressed on numerous and divergent tissue types. It is likely that there are multiple flt3/flk2-ligands; the current specification as filed teaches how to make and use only the particularly disclosed ligand, and does not enable claims to any and all possible flt3/flk2 ligands. The mere recitation of a name, i.e. flt3/flk2 ligand (or biological activity thereof) to describe the claimed invention is not sufficient to satisfy the statutes' requirement of adequately describing and setting forth the inventive concept. In order to avoid possible confusion over proteins with the same or similar names that may be found to have patentably different structure and/or utility, proteins claimed by a particular name should be further distinguished in the claims by conventional protein characterization according to known parameters, such as by molecular weight, pI, amino acid sequence information, whether the protein is a monomer or multimer, function(s) and/or activity, and/or other finger-printing techniques such as IR, NMR, or UV spectroscopy data and/or other known properties which would serve to distinguish the claimed protein from other flt3 ligands. In addition, in consideration of the discrepancies often encountered in the art between protein molecular weights when determined by different methods, whenever a molecular weight is recited to characterize a protein the claim should include the method by which it was determined, i.e. whether by SDS-PAGE, gel filtration or some other method, and whether reducing or non-reducing (native) conditions were used. Further, due to the definition of biological activity as found in the current specification as filed, the genus of "biologically active flt3/flk2-ligands" would include anti-flt3/flk2 antibodies, which antibodies would be capable of binding to the receptor, and, in view of the art, which recognizes that monoclonal antibodies may often mimic ligand binding and stimulate signal transduction via receptors, might even cause signal transduction via the flt3/flk2 receptor. Enablement of the current specification as filed is not commensurate in scope with claims which encompass nucleic acids encoding anti-flt3/flk2 antibodies.

Enablement of the current specification as filed is not commensurate in scope with claims to DNA molecules which hybridize under moderately stringent conditions to the cDNA disclosed in the current specification or alternatively are "derived" from the coding region of the *flt-3* ligand gene, and which encode a "biologically active" *flt3-L*. The specification defines biological activity as either the ability to bind to the *flt3/flk2* receptor or to cause the *flt3/flk2* receptor to transduce a signal. Claim 22(b) is therefore drawn to DNA molecules which hybridize under moderately stringent conditions to that disclosed, and encode a protein which binds *flt3/flk2*. However, there has been no characterization of what portions of the protein are necessary for such binding (other than the general characterization that it is the extracellular region which is functional), nor what specific alterations may be made in the protein without loss of binding activity. Therefore, applicants have failed to adequately teach how to make and use the DNA molecules of claim 22(b). With respect to claim 22(a), it is not clear how such cDNA is "derived" from the coding region of a *flt3-L* gene; such language not only encompasses both silent and non-silent base substitutions, but all other possible alterations which would not destroy binding activity; the current specification as filed does not teach how to make a commensurate number of such species. See M.P.E.P. §§ 706.03(n) and 706.03(z).

The deposit of biological organisms is considered by the Examiner to be necessary for enablement of the current invention as claimed in claim 23 (see 37 C.F.R. §1.808(a)). Examiner acknowledges the deposit of organisms under accession number ATCC 69286 under terms of the Budapest Treaty on International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure in partial compliance with this requirement (see the specification at page 31). However, in order to be fully compliant with the requirement, applicants must state that all restrictions on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent.

Claims 13-15, 22-26, 33-36 and 43 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.



Claims 22, 23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

~~All claims reciting as a limitation the property of biological activity are indefinite as the specification provides two different definitions for biological activity at page 682, and additionally demonstrates two other biological activities (the ability to stimulate cell proliferation in the presence of either IL-3 or IL-7) and it is not clear to which of these four types of activity the claims refer.~~

Claim 22 is further indefinite as it is not clear how the cDNA of part (a) is "derived" from the coding region of a flt3/flk2 ligand gene.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 13-43 are rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent Number 5,185,438 (Lemischka). Lemischka discloses the murine flk2 receptor, and suggests cloning and isolation of the ligand to the claimed receptor. See columns 6-7 and column 12 *et seq.* Additionally, Lemischka teaches that the receptor may be obtained from any mammal (Column 4, lines 21-24) and that the corresponding ligand "may be a growth factor that occurs naturally in a mammal, preferably the same mammal that produces the corresponding receptor" (col.7:1-3). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to obtain the flk2 ligand as suggested by Lemischka, to clone such, and to express such in appropriate host cells. One would have been motivated to do so by the disclosure of Lemischka that the ligand is useful for stimulating the proliferation of primitive mammalian hematopoietic stem cells (see Abstract). Lemischka teaches the necessary components for cloning vectors and host cells needed for cloning and expression of the ligand. The particular vectors recited in the claims are deemed to have been obvious choices known to the ordinary artisan, as evidenced by applicants admissions that they were known in the art and available to the ordinary artisan and contain the necessary elements as taught for example by Lemischka. With respect to those claims that recited the particular amino acid sequence encoded by the claimed DNA, it is noted that the sequence of amino acids one means of describing the protein; it would have been obvious to clone DNA encoding the protein as stated above, and the DNA having the property of encoding flt3-L would necessarily encode such amino acid sequences.

Claims 13-43 are rejected under 35 U.S.C. § 103 as being unpatentable over Flanagan and Leder (Cell 63:185) taken with Rosnet et al. (Oncogene 6:1641).

Flanagan et al. disclose a generally applicable method for the identification of an unknown ligand to a known receptor, wherein a fusion protein is constructed, consisting of the extracellular domain of the receptor fused to placental alkaline phosphatase, producing a soluble receptor affinity reagent with an enzyme tag that can be easily and sensitively traced (see abstract).

Specifically, Flanagan et al. used the disclosed method to clone the ligand to the c-kit receptor. Flanagan et al. do not suggest the use of their method for obtaining the ligand to the flt3 receptor.

At page 2 of the specification, applicants admit the disclosure by Rosnet et al. of the flt3  
5 receptor, and state that such is closely related to the c-fms and c-kit receptors. The Examiner further notes that Rosnet et al. disclose the desirability of obtaining the flt3 ligand at page 1648, second column. Also, it is noted that the murine flt3 disclosed by Rosnet et al. was obtained using a human flt3 clone as a hybridization probe (p.1649).

It would have been obvious to the person of ordinary skill in the art at the time the  
10 invention was made to use the method disclosed by Flanagan et al. to clone the ligand to the flt3 receptor disclosed by Rosnet et al. One of ordinary skill in the art would have been motivated to do so by Rosnet's indication of the desirability of doing so, and would have had a reasonable expectation of success in view of the admitted similarity between flt3 and c-kit. It would further have been obvious to obtain the human flt3 ligand, either by cloning analogously to the above,  
15 or alternatively, using the murine flt3 ligand as a hybridization probe. One of ordinary skill in the art would have been motivated to clone the human ligand for the same reasons as for the murine ligand, as well as for comparison to the murine ligand, and would have had a reasonable expectation of success at doing so, given that the required probes were available. Having obtained the DNA encoding the ligands, it would have been obvious to construct expression vectors  
20 comprising such (if the cloning were not in fact done so as to directly result in such) and to transform host cells for the maintenance of the cDNA clones and expression of the encoded protein. Such methods are ~~notoriously~~ old in the art, and are in fact necessary to expression cloning such as taught by Flanagan et al.

25 No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner


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should be directed to Lorraine M. Spector, Ph.D. whose telephone number is (703) 308-1793.  
Dr. Spector can normally be reached Monday through Friday, 8:00 A.M. to 4:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's  
supervisor, Ms. Garnette D. Draper, can be reached at (703)308-4232.

Any inquiry of a general nature or relating to the status of this application should be  
directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile  
transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal  
Mall 1 (CM1). The faxing of such papers must conform with the notices published in the  
Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see  
37 C.F.R. § 1.6(d)). The CM1 Fax Center number is (703) 305-3014. NOTE: If Applicant *does*  
submit a paper by fax, the original signed copy should be retained by applicant or applicant's  
representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the  
processing of duplicate papers in the Office.

  
GARNETTE D. DRAPER  
SUPERVISORY PRIMARY EXAMINER  
GROUP 1800

  
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